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Review Article

Recommended Measures for the Assessment of Cognitive and Physical Performance in Older Patients with Dementia: A Systematic Review

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Key Words

Dementia • Neuropsychological tests • Exercise tests • Tool use • Outcome measures • Systematic review

Abstract

Aim/Goal: To recommend a set of neuropsychological and physical exercise tests for researchers to assess cognition and physical fitness in clinical trials with older patients with dementia; to create consensus, decrease heterogeneity, and improve research quality. **Methods:** A literature search (2005–2011) yielded 89 randomized controlled trials. To provide information on test recommendations the frequency of test use, effect size of the test outcome, study quality, and psychometric properties of tests were analyzed. **Results:** Fifty-nine neuropsychological tests (cognitive domains: global cognition, executive functioning, memory, and attention) and 10 exercise tests (physical domains: endurance capacity, muscle strength, balance, and mobility) were found. **Conclusion:** The Severe Impairment Battery, Mini Mental State Examination, and Alzheimer Disease Assessment Scale – cognitive subscale were recommended to measure global cognition. The Verbal Fluency Test Category/Letters, Clock Drawing Test, and Trail Making Test-B were recommended to measure executive functioning. No specific memory test could be recommended. The Digit Span Forward, Digit Span Backward, and Trail Making Test-A were recommended to measure attention. As physical exercise tests, the Timed Up and Go and Six Meter Walk for mobility, the Six Minute Walk Distance for endurance capacity, and the Tinetti Balance Scale were recommended.

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Introduction

With the worldwide trend of an aging population, the number of patients with dementia will increase dramatically in the coming decades [1]. Dementia is characterized by a loss of neurons and atrophy of brain tissue [2–5]. Eventually, this leads to limitations in cognitive performance of executive functioning, memory, and attention [6, 7]. The neurodegenerative processes in the brain go hand in hand with limitations in physical performance of endurance capacity, muscle strength, balance, and mobility [6, 8]. Eventually, decline in cognitive performance and physical performance results in problems in activities of daily living and behavior, leading to institutionalization and a decreased quality of life [3, 9, 10]. Therefore, prevention of decline and preferably an improvement in both cognitive and physical performance in patients with dementia are of utmost importance.

With the growing impact of dementia on today's society, new treatments need to be developed that effectively reduce the limitations caused by a decline of cognitive and physical performance in patients with dementia [11]. Meta-analysis and systematic reviews reported that pharmacological (e.g. medication) and non-pharmacological (e.g. exercise) interventions may have a positive effect on cognition and physical functioning [12–18]. However, the individual studies in these reviews showed ambiguous results and the tests that measured cognitive and physical functioning appeared to show large heterogeneity. Consequently, the comparability of the outcomes of clinical trials is hampered [19]. Therefore, future intervention studies that aim to improve cognitive functioning, physical functioning, or a combination of both should strive to use a limited number of generally accepted, feasible, reliable, and valid tests that adequately cover the domains of cognitive and physical functioning in patients with dementia. This study is intended to contribute to this goal.

Recommendations on cognitive assessment tests for the purpose of diagnosing dementia were recently provided by Chaves et al. [20] and Young et al. [21]. Information regarding the tests on cognition that researchers should use for measuring treatment effects, however, is not available yet. To the authors' knowledge, recommendations regarding the use of exercise tests evaluating physical functioning in clinical trials are fully lacking.

The aim of this systematic review is to give up-to-date recommendations of both neuropsychological and physical exercise tests for researchers who have the aim to investigate treatment effects on cognition and physical functioning in older patients with dementia. Firstly, a comprehensive overview of tests on the basis of randomized controlled trials (RCTs) is presented. Frequently used neuropsychological and physical exercise tests are evaluated in relation with study quality of RCTs, nature of the interventions in RCTs, type of dementia that was studied, and sensitivity to change of the tests. Secondly, the reliability and validity of frequently used tests was reviewed.

Methods

Data Sources

Between August 2010 and August 2011, computer databases PubMed, EMBASE, Biological abstracts, Web of Science (ISI), PsycINFO, CINAHL, and Cochrane Library were searched for relevant studies published between 2005 and 2011. Limits for the searches in the computer databases were set on: clinical trial, humans, and age ≥ 65 years. Keywords in the search included terms from Medical Subject Headings (MESH) and EMBASE thesaurus (EMTREE). The following terms were used in the MESH database and EMTREE thesaurus: dementia, Alzheimer disease, vascular dementia, frontotemporal dementia, Lewy body disease, neuropsychological tests, and exercise tests. Keywords for dementia

(dementia OR Alzheimer disease OR vascular dementia OR frontotemporal dementia OR Lewy body disease) were combined (with 'AND') with terms that expressed the use of neuropsychological or exercise tests (neuropsychological tests OR exercise tests). In addition, reference lists of reviews regarding the subject were thoroughly hand searched for additional studies.

Inclusion Criteria

Studies were included if they met the following criteria: (1) the design was a RCT; (2) the participants had a diagnosis of dementia; (3) the participants were on average older than 65 years; (4) neuropsychological tests and/or exercise tests were used to measure the effects of an intervention, and (5) the study was written in English, German, French or Dutch.

Selection Process

After the literature search, a first selection of studies was made according to their titles, followed by a selection after reading the abstracts. Two reviewers (WB and MvH) independently performed both steps to identify those studies that met the inclusion criteria (agreement 94%, disagreement 6%). Disagreement was solved with full-text screening. Full-text analysis to check the inclusion criteria was performed for the studies identified in the preceding steps. Subsequently, reviews were hand searched for clinical trials that were not already found in the literature search. Finally, full-text analysis of and data extraction from the selected studies was performed.

Data Extraction

From the selected RCTs the following data were extracted: neuropsychological tests, physical exercise tests, type of dementia, sample size, and data regarding the intervention description (e.g. pharmacological, exercise). For each neuropsychological or physical exercise test the overall means and standard deviations were calculated from all RCTs that used a given test. Further, on the basis of the selected RCTs the overall means and standard deviations were calculated for age, baseline scores, and posttest scores.

Effect Size

In order to express the sensitivity to change for each neuropsychological or physical exercise test, Cohen's *d* effect sizes (ESs) for a test were calculated on the basis of the selected RCTs [22, 23]. If the mean and standard deviation of pretest and posttest were presented in the RCT, the following formula was used:

$$d = [(post_{exp} - pre_{exp}) - (post_{cont} - pre_{cont})] / \sqrt{[(s^2_{pre_{exp}} (n_{exp}) + s^2_{pre_{cont}} (n_{cont})) / (n_{exp} + n_{cont})] + [(s^2_{post_{exp}} (n_{exp}) + s^2_{post_{cont}} (n_{cont})) / (n_{exp} + n_{cont})] / 2} \quad [24]$$

If the means and standard deviations were not presented in the RCT, the *F* statistic was used with the following formula:

$$d = \sqrt{F \cdot [(n_{exp} + n_{cont}) / (n_{exp} \cdot n_{cont})] \cdot [(n_{exp} + n_{cont}) / (n_{exp} + n_{cont} - 2)]} \quad [24]$$

The overall ES was calculated as the mean of individual ESs weighted for the sample size. Cohen's benchmarks were used to indicate small ($d = 0.20$), medium ($d = 0.50$), and large ($d = 0.80$) ESs [22].

Study Quality

Study quality of each RCT that used a given test was assessed with the Physiotherapy Evidence Database (PEDro) [25]. According to the PEDro scoring system, a score of 9–10 was considered as excellent, a score of 6–8 as good, a score of 4–5 as moderate, and a score of 0–3

as poor [25]. For further analysis of neuropsychological and physical exercise tests in this review, the study quality of at least 5 RCTs must be good or excellent.

Reliability and Validity of Frequently Used Tests

After identifying the tests that were used in ≥ 5 good or excellent quality RCTs, a second search in PubMed was conducted through September 2011 to select the studies aimed at reporting the reliability and validity of these tests as evidenced in a population with dementia. Searches were performed by combining the terms ‘reliability’ OR ‘validity’ OR ‘reproducibility of results’ in combination with (with ‘AND’) keywords for dementia and the selected neuropsychological and physical exercise tests. By means of references, additional reliability and validity studies were searched.

Results

Study Characteristics

The literature searches for RCTs yielded a total of 840 potentially relevant publications. Eventually, 178 publications were full text screened of which 89 were excluded. A flowchart of the process is presented in figure 1. The results are described in two separate sections: (1) neuropsychological tests and (2) exercise tests. These sections describe the test use in RCTs (number of RCTs), test use related to intervention type, test use related to dementia type, ESs measured with the tests, and study quality of RCTs (PEDro). Table 1 describes 59 neuropsychological tests that covered the cognitive domains global cognition, executive functioning, memory, and attention. Thereafter, table 2 describes the psychometric data of the neuropsychological tests that were most often used. Finally, 10 exercise tests that covered the physical domains endurance capacity, muscle strength, balance, and mobility are presented in table 3.

Neuropsychological Tests

Frequency of Test Use

As is shown in table 1, global cognitive functioning was measured most often with the Mini Mental State Examination (MMSE) ($n = 54$), Alzheimer’s Disease Assessment Scale – cognitive subscale (ADAS-cog) ($n = 43$), and the Severe Impairment Battery (SIB) ($n = 8$). Tests for global cognitive functioning were used more often in comparison with neuropsychological tests that covered a specific cognitive area.

Thirty-two domain-specific neuropsychological tests were used in 63 RCTs, of which 7 tests were used in ≥ 5 RCTs. Executive functioning was measured with the Verbal Fluency Test Category ($n = 12$), Clock Drawing Test ($n = 6$), Verbal Fluency Test Letters ($n = 6$), and the Trail Making Test-B ($n = 5$). Attention was measured with the Digit Span Forward ($n = 8$), Digit Span Backward ($n = 7$), and Trail Making Test-A ($n = 6$).

In summary, global cognitive tests were used more often than neuropsychological tests that covered a specific cognitive area. Frequently used neuropsychological tests that were used in ≥ 5 RCTs covered the cognitive domains executive functioning and attention. Tests that were used in >5 RCTs which measured the cognitive domain memory were not found.

Dementia Type

A majority of the participants were diagnosed with Alzheimer’s disease (AD; 84%) or vascular dementia (VaD; 7%) (table 1). Neuropsychological tests that were only administered in RCTs with AD patients were the SIB (global cognitive functioning), Verbal Fluency Test Letters (executive functioning), Trail Making Test-A, Digit Span Forward, and Digit Span Backward (attention). Tests used in RCTs with AD or VaD patients were the MMSE and

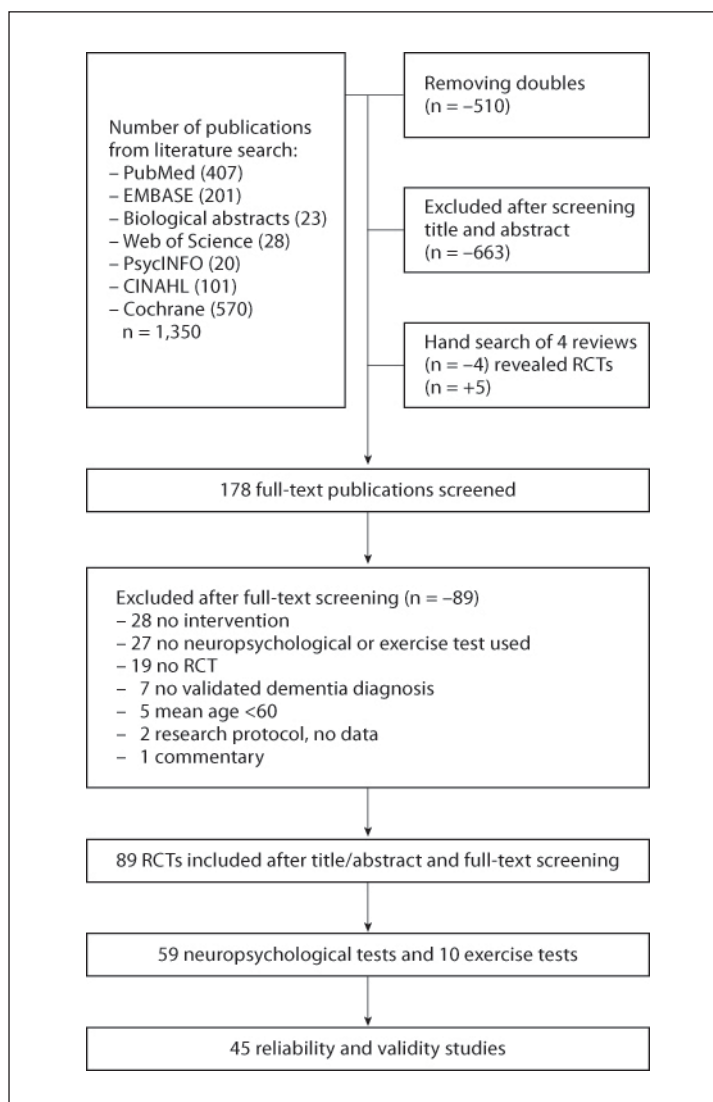


Fig. 1. Flow chart of literature search and study selection.

ADAS-cog (global cognitive functioning), Verbal Fluency Test Category, Clock Drawing Test, and Trail Making Test-B (executive functioning). Tests that were used in RCTs with only VaD, Lewy body disease, Pick's disease, and frontotemporal dementia patients were not found.

Effect Size

Pooled ESs ranged from small ($d = -0.16$) to large ($d = 1.58$). The global cognitive test Rapid Evaluation of Cognitive Functioning measured a large ES ($d = 1.12$). The global cognitive tests SIB ($d = 0.34$), ADAS-cog ($d = 0.19$), and MMSE ($d = 0.09$) showed small overall ESs. Overall ESs were small for both pharmacological and non-pharmacological RCTs. Furthermore, two neuropsychological tests that measured memory revealed large pooled ESs with the Visual Reproduction Test ($d = 1.58$) and the Syndrome Kurtz Test ($d = 0.82$). The Verbal Fluency Test Category that measures executive functioning measured a medium pooled ES ($d = 0.61$).

Table 1. Frequency of use of 59 neuropsychological tests (cognitive domain), descriptive statistics of the populations and RCTs in which these tests were used, the overall Cohen's *d* ES (small/medium/large) for the tests in these RCTs, and range of the study quality (PEDro) of RCTs (*n* = 63 in total) that used a given test

Neuropsychological test (test domain)	Studies, <i>n</i>	Participants, <i>n</i>	Intervention type (n of RCTs)	Mean age ^a ± SD years	Gender % ♀	Dementia type (%)	Mean baseline ^a ± SD	ES ^a	PEDro
MMSE (global functioning) [26–79]	54	7,606	pharmacological (39), cognitive (9), exercise (5), acupuncture (1)	75.8 ± 6.7	58	AD (80), VaD (18), LB (2)	8.0 ± 4.0	small	E (6), G (45), Mo (3), P (0)
ADAS-cog (global functioning) [26–28, 31, 32, 35, 39, 41, 43, 47, 48, 51, 54, 55, 58, 61, 63, 64, 67, 68, 70–72, 75, 77, 80–97]	43	10,133	pharmacological (37), cognitive (5), exercise (1)	74.4 ± 6.7	59	AD (81), VaD (17), LB (2)	24.4 ± 11.0	small	E (12), G (28), Mo (3), P (0)
Verbal Fluency Test Category (EF) [31, 36, 46, 47, 56, 98–104]	12	726	pharmacological (5), cognitive (2), exercise (1), hand movement (1), airway stimuli (1), CES (1), nerve stimuli (1)	74.2 ± 7.1	56	AD (47), VaD (29), n.r. (24)	10.9 ± 9.2	medium	E (4), G (6), Mo (1), P (1)
SIB (global functioning) [30, 37, 66, 73, 74, 105–107]	8	2,134	pharmacological (8)	76.6 ± 7.7	67	AD (100)	69.3 ± 19.2	small	E (3), G (5), Mo (0), P (0)
Digit Span Forward (attention) [31, 33, 49, 99, 101–104]	8	342	pharmacological (1), cognitive (2), exercise (1), hand movement (1), airway stimuli (1), CES (1), nerve stimuli (1)	82.6 ± 6.7	55	AD (76), n.r. (24)	5.4 ± 2.3	small	E (3), G (4), Mo (0), P (1)
Digit Span Backward (attention) [31, 49, 99, 101–104]	7	280	cognitive (2), exercise (1), hand movement (1), airway stimuli (1), CES (1), nerve stimuli (1)	82.2 ± 6.5	50	AD (44), n.r. (56)	3.9 ± 1.5	small	E (3), G (3), Mo (0), P (1)
Clock Drawing Test (EF) [42, 50, 56, 95, 100, 108]	6	1,674	pharmacological (5), exercise (1)	72.1 ± 7.7	68	AD (82), VaD (17), LB (1)	4.5 ± 3.2	small	E (3), G (2), M (0), P (1)
Trail Making Test-A (attention) [31, 42, 83, 101–103]	6	1,502	pharmacological (3), cognitive (1), airway stimuli (1), CES (1)	73.8 ± 8.0	67	AD (98), FTD (2)	161 ± 82.5	small	E (1), G (4), Mo (0), P (1)
Verbal Fluency Test Letters (EF) [36, 56, 99, 101–103]	6	319	pharmacological (1), cognitive (1), exercise (1), airway stimuli (1), CES (1), nerve stimuli (1)	78.9 ± 5.6	44	AD (56), PD (44)	16.3 ± 4.6	small	E (2), G (3), Mo (0), P (1)
Trail Making Test-B (EF) [27, 31, 47, 98, 101]	5	214	pharmacological (3), cognitive (1), airway stimuli (1)	73.9 ± 6.2	58	AD (100)	242.8 ± 91.3	small	E (2), G (3), Mo (0), P (0)
Logical Memory Test – immediate recall (memory) [28, 49, 69, 70]	4	277	pharmacological (2), cognitive (2)	75.6 ± 6.8	69	AD (100)	11.5 ± 4.7	small	E (2), G (2), Mo (0), P (0)
Logical Memory Test – delayed recognition (memory) [28, 49, 69, 70]	4	277	pharmacological (2), cognitive (2)	75.6 ± 6.8	69	AD (100)	2.8 ± 2.9	small	E (2), G (2), Mo (0), P (0)
Logical Memory Test – delayed recall (memory) [28, 49, 69, 70]	4	277	pharmacological (2), cognitive (2)	75.6 ± 6.8	69	AD (100)	0.9 ± 1.6	small	E (2), G (2), Mo (0), P (0)
Eight Word Test – immediate recall (memory) [99, 102–104]	4	196	exercise (1), hand movement (1), CES (1), nerve stimuli (1)	84.7 ± 6.1	62	AD (38), n.r. (62)	17.6 ± 8.1	small	E (2), G (1), Mo (0), P (1)
Eight Word Test – delayed recall (memory) [99, 102–104]	4	196	exercise (1), hand movement (1), CES (1), nerve stimuli (1)	84.7 ± 6.1	62	AD (38), n.r. (62)	0.35 ± 0.94	small	E (2), G (1), Mo (0), P (1)
Eight Word Test – delayed recognition (memory) [99, 102–104]	4	196	exercise (1), hand movement (1), CES (1), nerve stimuli (1)	84.7 ± 6.1	62	AD (38), n.r. (62)	10.7 ± 3.9	small	E (2), G (1), Mo (0), P (1)
Rivermead Behavioral Memory Test – face recognition (memory) [99, 102–104]	4	196	exercise (1), hand movement (1), CES (1), nerve stimuli (1)	84.6 ± 6.1	59	AD (54), n.r. (46)	6.6 ± 3.5	small	E (2), G (1), Mo (0), P (1)
Rivermead Behavioral Memory Test – picture recognition (memory) [99, 102–104]	4	196	exercise (1), hand movement (1), CES (1), nerve stimuli (1)	84.6 ± 6.1	59	AD (54), n.r. (46)	12.2 ± 6.3	small	E (2), G (1), Mo (0), P (1)

Table 1 (continued)

Neuropsychological test (test domain)	Studies, n	Participants, n	Intervention type (n of RCTs)	Mean age ^a ± SD years	Gender % ♀	Dementia type (%)	Mean baseline ^a ± SD	ES ^a	PEDro
Mattis Dementia Rating Scale (global functioning) [46, 50, 101]	3	105	pharmacological (2), airway stimuli (1)	77.1 ± 7.3	67	AD (78), LB (22)	108.8 ± 15.7	small	E (1), G (2), Mo (0), P (0)
Modified Boston Naming Test (language) [31, 49, 69]	3	62	pharmacological (1), cognitive (2)	77.4 ± 7.8	76	AD (100)	10.4 ± 4.6	small	E (1), G (2), Mo (0), P (0)
Syndrome Kurtz Test (attention/memory) [52, 100]	2	290	pharmacological (2)	65.2 ± 7.5	64	AD (38), VaD (62)	16.0 ± 3.7	large	E (2), G (0), Mo (0), P (0)
Digit Symbol Test (attention) [42, 101]	2	273	pharmacological (1), airway stimuli (1)	73.8 ± 8.0	72	AD (100)	11.7 ± 5.8	small	E (1), G (1), Mo (0), P (0)
STROOP color-word interference (EF) [98, 101]	2	67	pharmacological (1), airway stimuli (1)	77.7 ± 6.6	54	AD (100)	65.5 ± 41.2	small	E (1), G (1), Mo (0), P (0)
Cambridge Neuropsychological Test Battery (global functioning) [78, 109]	2	50	pharmacological (1), exercise stimuli (1)	71.2 ± 8.1	56	AD (65), FTD (35)	–	–	E (0), G (1), Mo (1), P (0)
Visual Memory Span (memory) [102, 103]	2	38	CES (1), nerve stimuli (1)	84.4 ± 6.3	59	AD (100)	9.0 ± 3.8	small	E (0), G (1), Mo (0), P (1)
Selective Reminding Test (memory) [28, 49]	2	35	cognitive (2)	72.9 ± 7.1	89	AD (100)	13.3 ± 12.4	small	E (2), G (0), Mo (0), P (0)
Block Design Test (EF) [84, 98]	2	31	pharmacological (2)	72.8 ± 6.8	0	AD (100)	45.5 ± 14.9	small	E (2), G (0), Mo (0), P (0)
The Executive Interview (EF) [81]	1	363	pharmacological (1)	72.3 ± 9.0	38	VaD (100)	18.3 ± 7.0	small	E (0), G (1), Mo (0), P (0)
Cambridge Cognitive Examination (global functioning) [38]	1	179	pharmacological (1)	87.4 ± 6.0	57	AD (100)	69.0 ± 13.0	small	E (0), G (1), Mo (0), P (0)
Age-Adjusted Concentration Task (attention) [65]	1	65	pharmacological (1)	77.8 ± 5.6	58	AD (66), VaD (11)	–	small	E (0), G (1), Mo (0), P (0)
Auditory Verbal Learning Test – Chinese version (memory) [33]	1	62	pharmacological (1)	83.9 ± 7.6	80	AD (100)	2.6 ± 1.5	small	E (0), G (0), Mo (1), P (0)
Stop Signal Reaction Time (attention) [104]	1	61	hand movement (1)	84.7 ± 5.1	58	n.r.	–	–	E (0), G (0), Mo (1), P (0)
Attention Network Task (attention) [104]	1	61	hand movement (1)	84.7 ± 5.1	58	n.r.	–	–	E (0), G (0), Mo (1), P (0)
Hasegawa's Evaluation of Cognitive Functioning (global functioning) [76]	1	60	acupuncture (1)	66.7 ± 10.5	34	VaD (100)	11.3 ± 4.5	small	E (0), G (0), Mo (1), P (0)
Cognitive Abilities Screening Instrument (global functioning) [40]	1	60	cognitive (1)	82.3 ± 5.9	67	VaD (100)	54.6 ± 15.3	small	E (1), G (0), Mo (0), P (0)
Digit Cancellation Task (attention) [101]	1	52	airway stimuli (1)	78.2 ± 7.2	69	AD (100)	–	–	E (0), G (0), Mo (1), P (0)
Hopkins Verbal Learning Test – revised (memory) [101]	1	52	airway stimuli (1)	78.2 ± 7.2	69	AD (100)	3.3 ± 1.5	small	E (0), G (1), Mo (0), P (0)
Wisconsin Card Sorting Test (EF) [101]	1	52	airway stimuli (1)	78.2 ± 7.2	69	AD (100)	–	–	E (0), G (1), Mo (0), P (0)
The Executive Clock Drawing Task 1 (EF) [110]	1	51	pharmacological (1)	77.9 ± 7.0	55	AD (100)	6.2 ± 3.7	small	E (0), G (1), Mo (0), P (0)
The Executive Clock Drawing Task 2 (EF) [110]	1	51	pharmacological (1)	77.9 ± 7.0	55	AD (100)	10.7 ± 3.0	small	E (0), G (1), Mo (0), P (0)

Table 1 (continued)

Neuropsychological test (test domain)	Studies, n	Participants, n	Intervention type (n of RCTs)	Mean age ^a ± SD years	Gender % ♀	Dementia type (%)	Mean baseline ^a ± SD	ES ^a	PEDro
Rey-Osterrieth Complex Figure Test – Copy (EF) [36]	1	32	cognitive (1)	73.0 ± 7.2	62	AD (100)	16.5 ± 14.6	small	E (0), G (1), Mo (0), P (0)
Rey-Osterrieth Complex Figure Test – Recall (EF) [36]	1	32	cognitive (1)	73.0 ± 7.2	62	AD (100)	1.2 ± 2.0	small	E (0), G (1), Mo (0), P (0)
Three Dimensional Constructional Praxis (constructive abilities) [69]	1	32	cognitive (1)	73.0 ± 7.2	62	AD (100)	11.9 ± 0.48	–	E (0), G (1), Mo (0), P (0)
Extended Rivermead Behavioral Memory Test – profile (memory) [36]	1	32	cognitive (1)	73.0 ± 7.2	62	AD (100)	1.2 ± 1.3	small	E (0), G (1), Mo (0), P (0)
Attention Matrices Test (attention) [36]	1	32	cognitive (1)	73.0 ± 7.2	62	AD (100)	32.4 ± 11.7	small	E (0), G (1), Mo (0), P (0)
Visual Reproduction 1 (memory) [28]	1	16	cognitive (1)	73.8 ± 4.8	82	AD (100)	13.8 ± 3.6	large	E (1), G (0), Mo (0), P (0)
Rapid Evaluation of Cognitive Functioning (global functioning) [111]	1	31	exercise (1)	81.8 ± 5.3	74	AD (100)	27.6 ± 6.8	large	E (0), G (1), Mo (0), P (0)
Developmental Test of Visual Motor Integration (perception) [84]	1	16	pharmacological (1)	69.8 ± 8.6	0	AD (100)	18.1 ± 2.7	small	E (1), G (0), Mo (0), P (0)
Visual Reproduction 2 (memory) [28]	1	16	cognitive (1)	73.8 ± 4.8	82	AD (100)	1.3 ± 2.8	small	E (1), G (0), Mo (0), P (0)
Judgment of Line Orientation (constructive abilities) [84]	1	16	pharmacological (1)	69.8 ± 8.6	0	AD (100)	18.2 ± 8.9	small	E (1), G (0), Mo (0), P (0)
California Verbal Learning Test – delayed recall (memory) [84]	1	16	pharmacological (1)	69.8 ± 8.6	0	AD (100)	1.6 ± 1.9	small	E (1), G (0), Mo (0), P (0)
Recognition Memory Test – faces (memory) [28]	1	16	cognitive (1)	73.8 ± 4.8	82	AD (100)	28.0 ± 5.9	small	E (1), G (0), Mo (0), P (0)
Benton Visual Retention Test (memory) [49]	1	19	cognitive (1)	72.1 ± 8.5	95	AD (100)	1.9 ± 1.8	small	E (1), G (0), Mo (0), P (0)
Recognition Memory Test – words (memory) [28]	1	16	cognitive (1)	73.8 ± 4.8	82	AD (100)	32.7 ± 8.9	small	E (1), G (0), Mo (0), P (0)
Milan Overall Dementia Assessment (global functioning) [59]	1	16	cognitive (1)	68.0 ± 6.5	48	AD (100)	–	small	E (0), G (0), Mo (1), P (0)
Proactive Interference Test (memory) [98]	1	15	pharmacological (1)	76.0 ± 4.0	0	AD (100)	7.7 ± 4.2	small	E (1), G (0), Mo (0), P (0)
Route Test (EF) [98]	1	15	pharmacological (1)	76.0 ± 4.0	0	AD (100)	15.1 ± 9.6	small	E (1), G (0), Mo (0), P (0)
Story Recall Test (memory) [98]	1	15	pharmacological (1)	76.0 ± 4.0	0	AD (100)	12.0 ± 13.2	small	E (1), G (0), Mo (0), P (0)
Fuld Object and Memory Evaluation (memory) [31]	1	13	cognitive (1)	73.3 ± 6.4	69	AD (100)	24.7 ± 11.1	small	E (0), G (1), Mo (0), P (0)

E = Excellent (9–10); G = good (6–8); Mo = moderate (4–5); P = poor (0–3); EF = executive functioning; CES = cranial electrostimulation; LB = Lewy body disease; PD = Pick's disease; FTD = frontotemporal dementia; n.r. = not reported. ^a Pooled and weighted data as a function of the number of participants.

Table 2. Reliability, validity, and summary of the psychometric properties of 10 selected neuropsychological tests (cognitive domain) that were used in ≥ 5 good- or high-quality RCTs

Neuropsychological test (domain)	Reliability	Validity	Summary
MMSE (global functioning)	test-retest reliability (ICC): 0.85–0.90 [112]; 0.89 [113]; 0.92 [114]; 0.69 [115]; 0.89 [116]; 0.80 [117]; 0.86 [118] inter-rater reliability: ICC = 0.69–0.78 [115]; κ = 0.63 [114]; ICC = 0.69 [115] internal consistency (α): 0.54–0.96 [119]; 0.78 [120]; 0.77 [121]; 0.68 [122]; 0.96 [123]; 0.90 [124]; 0.81 [125]	concurrent validity with Wechsler adult intelligence scale verbal IQ (r = 0.78) and performance IQ (r = 0.66) [113]	reliable and valid test in dementia patients; there is a floor effect in severe dementia patients [119]; sensitivity to change over time is questionable because small changes could be due to measurement errors [125]
ADAS-cog (global functioning)	test-retest reliability (ICC): 0.91–0.95 [126]; 0.65–0.92 [127]; 0.90 [128]; 0.93 [129]; 0.96 [130]; 0.86–0.96 [131]; 0.90 [132] inter-rater reliability: ICC = 0.65–0.95 [131]; κ = 0.99 [130]; ICC = 0.98–0.99 [126]; ICC = 0.97–0.99 [127]; κ = 0.99 [133] internal consistency (α): 0.65–0.91 [131]; 0.87 [130]; 0.52–0.87 [126]; 0.96 [128]; 0.15–0.93 [134]; 0.81 [129]; 0.84 [135]	concurrent validity with MMSE (r = –0.63) [135]	reliable and valid test in patients with mild to moderate dementia
Verbal Fluency Test Category (EF)	–	–	no information available about reliability and validity for dementia patients
SIB (global functioning)	test-retest reliability (ICC): 0.79 [136]; 0.97 [137]; 0.87 [138]; 0.90 [139]; 0.93 [135] inter-rater reliability: Spearman's ρ = 0.85 [140]; Spearman's ρ = 0.97 [137]; ICC = 0.99 [138] internal consistency (α): 0.97 [136]; 0.97 [140]; 0.98 [137]	concurrent validity with MMSE (r = 0.85) [140]	reliable and valid test in dementia patients [140]; this test is sensitive to changes in patients with moderate to severe dementia (MMSE 0–12) [140]; promising test for follow-up in therapeutic trials [138]
Digit Span Forward (attention)	–	–	no information available about reliability and validity for dementia patients; Digit Span Test as a sub-test in the SIB was sensitive to change in dementia patients [141]
Verbal Fluency Test Letters (EF)	–	–	no information available about reliability and validity for dementia patients
Digit Span Backward (attention)	–	–	no information available about reliability and validity for dementia patients; Digit Span Test as a sub-test in the SIB was sensitive to change in dementia patients [141]
Clock Drawing Test (EF)	test-retest reliability (ICC): 0.70–0.78 [142] inter-rater reliability: ICC = 0.82 [143]; ICC = 0.92 [144]; ICC = 0.88 [145]; κ = 0.82–0.94 [146]; κ = 0.94 [147]; κ = 0.63–1.0 [148] internal consistency (α): 0.75 [142]	concurrent validity with MMSE (r = 0.13) [142]	reliable test in dementia patients
Trail Making Test-A (attention)	–	–	no information available about reliability and validity for dementia patients
Trail Making Test-B (EF)	–	–	no information available about reliability and validity for dementia patients

EF = Executive functioning.

Study Quality

According to the PEDro scale, the study quality of RCTs that used neuropsychological tests ranged from 2 (poor) to 10 (excellent). Three RCTs with poor study quality used the Verbal Fluency Test Category, Digit Span Forward, Digit Span Backward, Clock Drawing Test, Trail Making Test-A, and Verbal Fluency Test Letters. Because these tests were also found in RCTs with excellent and good study quality, this had no effect on the selection process of these neuropsychological tests.

Table 3. Frequency of use of 10 physical exercise tests (physical exercise domain), descriptive statistics of the populations and RCTs in which these tests were used, the overall Cohen's d ES (small/medium/large) for the tests in these RCTs, and range of the study quality (PEDro) of RCTs (n = 13 in total) that used a given test

Physical exercise test (test domain)	Studies, n	Participants, n	Intervention type (n of RCTs)	Mean age ^a ± SD years	Gender % ♀	Dementia type (%)	Mean baseline ^a ± SD	ES ^a	PEDro
Timed Up and Go Test (mobility) [45, 150, 151]	3	179	Exercise (3)	81.9 ± 7.3	71	AD (100)	17.1 ± 7.5	small	E (0), G (2), Mo (1), P (0)
Six Minute Walk Distance (endurance capacity) [45, 77]	2	105	Exercise (2)	77.6 ± 6.6	65	AD (39), VaD (16), LB (16), n.r. (29)	221.0 ± 82.6	medium	E (0), G (2), Mo (0), P (0)
Functional Reach Test (flexibility) [77, 150]	2	94	Exercise (2)	76.6 ± 6.6	52	AD (82), VaD (18)	20.4 ± 8.1	small	E (0), G (2), Mo (0), P (0)
Six Meter Walk (mobility) [151]	1	134	Exercise (1)	83.0 ± 7.4	75	AD (100)	0.4 ± 0.2	medium	E (0), G (1), Mo (0), P (0)
Abnormal One-Leg Balance (balance) [151]	1	134	Exercise (1)	83.0 ± 7.4	75	AD (100)	–	–	E (0), G (1), Mo (0), P (0)
Tinetti Balance Scale (balance) [56]	1	116	Pharmacological (1)	73.4 ± 2.5	62	AD (100)	8.5 ± 1.2	large	E (1), G (0), Mo (0), P (0)
Five Times Sit to Stand (leg strength) [150]	1	29	Exercise (1)	76.9 ± 6.7	51	AD (72), LB (28)	18.9 ± 7.2	small	E (0), G (1), Mo (0), P (0)
Berg Balance Scale (balance) [77]	1	85	Exercise (1)	76.6 ± 6.5	52	AD (61), VaD (20), LB (19)	47.5 ± 16.9	small	E (0), G (1), Mo (0), P (0)
30 Second Chair Stand (leg strength) [152]	1	16	Exercise (1)	74.5 ± –	37	AD (100)	–	–	E (0), G (0), Mo (1), P (0)
Two Minute Step Test (endurance capacity) [152]	1	16	Exercise (1)	74.5 ± –	37	AD (100)	–	–	E (0), G (0), Mo (1), P (0)

E = Excellent (9–10); G = good (6–8); Mo = moderate (4–5); P = poor (0–3); LB = Lewy body disease; n.r. = not reported. ^a Weighted data as a function of the number of participants.

Reliability and Validity

Table 2 presents the reliability and validity of 10 neuropsychological tests that were used in ≥5 good or excellent RCTs. The global cognitive tests MMSE, ADAS-cog, and SIB were found to be reliable and valid tools for dementia patients. The Clock Drawing Test was reliable but showed an unsatisfactory concurrent validity with other tests that measured executive functioning [149]. No reliability or validity studies with dementia patients were found for the Verbal Fluency Test Category, Verbal Fluency Test Letters, Trail Making Test-B, Digit Span Forward, Digit Span Backward, and Trail Making Test-A.

Table 4. Recommendations of global and specific neuropsychological tests ordered on the basis of frequency of test use, overall ES, study quality, reliability, and validity for global cognitive functioning, executive functioning, memory, and attention

Global functioning	Executive functioning	Memory	Attention
1 SIB ^{a-d}	Verbal Fluency Test Category ^{a-c}	Visual Reproduction Test ^{*, b, c}	Digit Span Forward ^{a, c}
2 MMSE ^{a, c, d}	Clock Drawing Test ^{a, c, d}	Eight Word Test ^{*, c}	Digit Span Backward ^{a, c}
3 ADAS-cog ^{a, c, d}	Verbal Fluency Test Letters ^{a, c}	Logical Memory Test ^{*, c}	Trail Making Test-A ^{a, c}
4 Rapid Evaluation of Cognitive Functioning ^{*, b-d}	Trail Making Test-B ^{a, c}		

^a Frequently used in RCTs (feasibility). ^b Able to measure an effect (sensitivity to change). ^c Test was used in excellent/good quality RCTs (PEDro). ^d Reliable/valid in dementia patients.
* More research is needed to recommend these tests.

Exercise Tests

Frequency of Test Use

Ten different exercise tests were used in 13 RCTs (table 3). These tests measured the physical exercise domains endurance capacity with the Six Minute Walk Distance and Two Minute Step Test; muscle strength with the Five Times Sit To Stand and 30 Second Chair Stand; balance with the Tinetti Balance Scale, Abnormal One-Leg Balance, and Berg Balance Scale; mobility with the Timed Up and Go and Six Meter Walk, and flexibility with the Functional Reach Test. All physical exercise tests were used in non-pharmacological RCTs, except for the Tinetti Balance Scale that was also used in 1 pharmacological RCT.

Dementia Type

A majority of the participants were diagnosed with AD (84%) or VaD (6%). Six exercise tests were used only in AD patients and covered the physical exercise domains endurance capacity (Two Minute Step Test), muscle strength (30 Second Chair Stand), balance (Tinetti Balance Scale, Abnormal One-Leg Balance), and mobility (Timed Up and Go, Six Meter Walk). Physical exercise tests were not used in RCTs only including VaD patients. In RCTs that included both AD and VaD patients, 3 physical exercise tests measured the physical exercise domains endurance capacity (Six Minute Walk Distance), flexibility (Functional Reach Test), and balance (Berg Balance Scale).

Study Quality

The study quality of RCTs ranged from 5 (moderate) to 9 (excellent). Only the Tinetti Balance Scale was used in a RCT with excellent study quality (PEDro 9).

Effect Size

Pooled ESs of RCTs ranged from small ($d = 0.02$) to large ($d = 0.87$). A large ES was found with the Tinetti Balance Scale ($d = 0.87$). Medium ESs were found with the Six Meter Walk ($d = 0.58$) and the Six Minute Walk Distance ($d = 0.51$).

Table 5. Domain-specific physical exercise tests, ordered on the basis of frequency of tests use, ES, study quality, reliability, and validity for the physical exercise domains endurance capacity, muscle strength, balance, and mobility

	Endurance capacity	Muscle strength*	Balance	Mobility
1	Six Minute Walk Distance*, a–c	Five Times Sit to Stand*	Tinetti Balance Scale*, a, b	Timed Up and Go*, b, c
2		30 Second Chair Stand*		Six Meter Walk*, a–c

^a Able to measure an effect (sensitivity to change). ^b Test was used in excellent/good-quality RCTs (PEDro). ^c Reliable/valid in dementia patients. * More research is needed to recommend these tests.

Reliability and Validity

The Timed Up and Go [intraclass correlation (ICC) = 0.985–0.988], Six Minute Walk Distance (ICC = 0.982–0.987), and Six Meter Walk (ICC = 0.973–0.977) showed excellent test-retest values for older patients with dementia [153]. For the remaining physical exercise tests that are presented in table 3, no psychometric studies for the reliability and validity with dementia patients were found.

Discussion

To improve the study quality and increase comparability of clinical trials and observational studies, researchers should strive to use a limited number of generally accepted, feasible, reliable, and valid tests that cover the domains of cognitive and physical functioning. Following previous studies that recommended neuropsychological tests for the diagnoses of dementia [20, 21] and studies that stated the importance of physical exercise to attenuate cognitive impairment in older patients with dementia [154], the aim of the current review was to give up-to-date recommendations of both neuropsychological and physical exercise tests for high-quality experimental research with older patients with dementia.

Neuropsychological Tests

This study revealed 59 different neuropsychological tests that were used in 63 RCTs. This confirms the assumption that there is a large heterogeneity in neuropsychological test use in RCTs with older patients with dementia. The results showed that global cognitive tests were used more often in comparison with neuropsychological tests that measured one specific cognitive domain.

In particular, the global cognitive tests MMSE, ADAS-cog, and the SIB were standing out because of their excellent reliability and validity (table 2), and were often used in high-quality RCTs which suggest that they are feasible. However, for all 3 tests the sensitivity to change was low. In line with this, the sensitivity to change of the MMSE and ADAS-cog was also challenged in other studies [140], because changes in performance measured with these tests can easily be caused by small measurement errors [125]. For the SIB, research [140] showed that this test is sensitive to change in patients with severe dementia. Altogether, on the basis of feasibility, sensitivity, reliability, and validity we recommend the use of the SIB in RCTs to measure global cognitive treatment effects.

Memory tests could not be selected in this review due to the large heterogeneity that was found in memory test use. Earlier work on memory tests for diagnosing dementia showed that verbal memory, visual memory, and non-verbal memory can be assessed with several tests [20]. Most of these tests were only used once in RCTs between 2005 and 2011, and 1 test

(Word List of the Consortium to Establish a Registry for Alzheimer's disease) was not used at all in RCTs over that period. Additionally, because these tests were specifically recommended for diagnosis of dementia, we suggest that it is not feasible to measure effects over time with these tests. Furthermore, studies that investigated the psychometric properties of these memory tests are lacking.

To measure executive functioning, we recommend the use of the Verbal Fluency Test Category, Clock Drawing Test, Verbal Fluency Test Letters, and the Trail Making Test-B because they were frequently used in good- or excellent-quality RCTs. However, we found that only the Verbal Fluency Test Category was able to detect change, and only the Clock Drawing Test was found to be reliable for the population of older dementia patients (table 2). Since information and psychometric quality is in many cases still insufficient, the recommended selection should be used with care and further evaluation of these tests is needed.

For attention we recommend the Digit Span Forward, Digit Span Backward, and Trail Making Test-A because of their frequent use in high-quality studies. However, no studies were found that investigated the psychometric properties of these tests. Furthermore, the results showed that the sensitivity to change was small.

Table 4 sums up the best currently available tests used in international intervention studies with older persons with dementia. Although they are widely applied, it was shown that the recommended neuropsychological tests lack psychometric studies. Therefore, future research into the psychometric quality of the tests found in this review is essential. The recommended selection of currently optimal cognitive tests should be used with care. Researchers are advised to select the recommended tests that most closely fit their study objectives.

Physical Exercise Tests

This review found 10 different exercise tests that covered the domains endurance capacity, muscle strength, balance, and mobility. However, there is a large heterogeneity in tests used and none of the tests were used frequently enough in RCTs to recommend them. Preliminary recommendations based on the results of this review may be a first step for the selection of exercise tests.

For endurance capacity, the results showed that the Six Minute Walk Distance is reliable [153] and sensitive to change. Muscle strength was measured with the Five Times Sit to Stand and the 30 Second Chair Stand. However, no studies were available that investigated the feasibility and psychometric properties for these tests. For balance, results showed that the Tinetti Balance Scale was sensitive to change, but again no studies were available that investigated the feasibility and psychometric properties. Mobility was measured with the Six Meter Walk and the Timed Up and Go. The results showed that both tests are reliable [153]. However, only the Six Meter Walk was sensitive to change. Based on the limited information at hand, the best exercise tests available so far are summed up in table 5.

Because of the importance of physical functioning in the disease process of dementia [154], it is essential that future research obtains more information on the feasibility, sensitivity to change, reliability, and validity of physical exercise tests that were found in this review. Since this information is in many cases still insufficient, the recommendation of optimal physical tests should be used with care.

Conclusion

This review mapped the large heterogeneity in cognitive and physical functioning tests used in international intervention studies with older persons with dementia. The provided neuropsychological (table 4) and exercise (table 5) test recommendations from this system-

atic analysis may lead to a more evidence-based choice of tests that better fit the research questions of future studies. Since information on psychometric quality is in many cases still insufficient, the recommended selection of currently optimal cognitive and physical tests should be used with care. Researchers are advised to select those recommended tests that most closely fit their study objectives.

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